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DOI:

[10.1016/j.thromres.2017.12.021](https://doi.org/10.1016/j.thromres.2017.12.021)

*Document Version*

Publisher's PDF, also known as Version of record

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

Bartoli-Abdou, J., Patel, J. P., Crawshaw, J., Vadher, B., Brown, A., Roberts, L. N., Patel, R. K., Arya, R., & Auyeung, V. (2018). Exploration of adherence and patient experiences with DOACs one year after switching from vitamin-K antagonists- insights from the switching study. *Thrombosis Research*, 162, 62-68.  
<https://doi.org/10.1016/j.thromres.2017.12.021>

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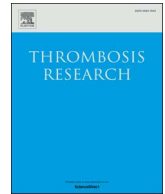
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## Full Length Article

## Exploration of adherence and patient experiences with DOACs one year after switching from vitamin-K antagonists- insights from the switching study



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## ARTICLE INFO

## Keywords:

Warfarin  
Vitamin- K antagonists  
Direct oral anticoagulant  
DOAC  
Adherence  
Patient care  
Atrial fibrillation  
Venous thromboembolism  
Quality of life

## ABSTRACT

**Background:** Current UK and European guidelines recommend anticoagulated patients prescribed warfarin with time in therapeutic range (TTR) < 65% be considered for DOAC therapy. There has been considerable concern that adherence with DOACs may be poor compared with warfarin. Little is known about the patient experience of switching from warfarin to DOAC and how patients manage their DOAC long term. Our aim was to conduct focus groups exploring patient's previous experiences with warfarin, their current experience with DOACs, their adherence to DOACs and the long-term service provision they envisage.

**Methods:** Patients enrolled on the Switching Study who had been switched from warfarin to a DOAC > 1 year previously were invited to participate in focus groups. Two focus groups for atrial fibrillation (AF) and two for secondary prevention of venous thromboembolism (VTE) patients were held at anticoagulation clinics in South London, UK. Data was analysed using framework analysis to extract dominant themes.

**Results:** Five VTE patients and 15 AF patients attended the focus groups. Dominant themes that emerged were: indication specific anticoagulation prioritisation, warfarin as a necessary inconvenience, DOACs as the anticoagulant of choice, concerns regarding DOAC monitoring, high adherence to DOACs and desire for long-term access to specialist anticoagulation services.

**Discussion:** VTE patients prioritised anticoagulation over other therapies whereas AF patients did not. All participants reported high levels of adherence to DOACs. Patients derived confidence from long-term management in specialist anticoagulation clinics stating a preference to be managed in such a service.

## 1. Introduction

Since their introduction into clinical practice, direct oral anticoagulants (DOACs) are being increasingly prescribed for stroke prevention in atrial fibrillation (AF) and the treatment and secondary prevention of venous thromboembolism (VTE) [1]. In phase III clinical trials apixaban dabigatran, edoxaban and rivaroxaban were shown to be at least non-inferior to traditional vitamin-K antagonists (VKAs) such as warfarin [2–12]. Relative advantages of DOACs compared to VKAs include: a predictable pharmacokinetic profile enabling fixed dosing and infrequent laboratory monitoring, limited drug- drug interactions and insignificant drug- food interactions [13]. However, although DOACs may have a lower burden on both patients and healthcare providers, they present new challenges for anticoagulation services.

With VKAs, patients are routinely required to undergo laboratory monitoring for international normalised ratio (INR) tests to ensure safe

and effective care. This provides patients with the opportunity to monitor their results over time, providing direct feedback on their medicines taking behaviour. This is not possible with DOACs. Out of range INR results can be investigated for underlying causes in collaboration with anticoagulant clinic staff; offering opportunities for patients to discuss issues surrounding their VKA management with a specialist, allowing for educational opportunities as well as timely resolution of any problems. One such issue is medication adherence. Frequent INR monitoring provides an indication to clinicians regarding patient adherence. Opportunities arise to broach issues surrounding not only adherence but also the impact of the disease and the benefits of therapy. As this model of care is not required with DOACs, there is significant concern that this lack of routine monitoring and regular engagement with anticoagulation services may lead to worse adherence to DOACs compared to VKAs [14–16].

Whilst some work has been done to describe adherence to DOACs

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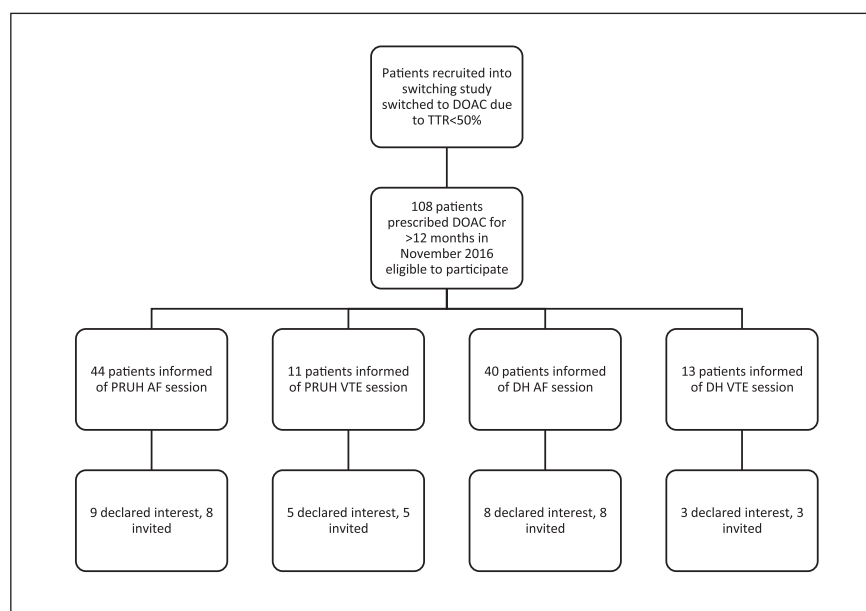


Fig. 1. Focus group pathway.

over recent years [17,18], including amongst those that have switched therapy from VKA to DOAC [19], there is very little narrative evidence exploring adherence to DOACs and the patient's journey from initiation to discharge from secondary care services and beyond.

The new age of DOACs presents a significant paradigm shift for practitioners and patients alike. In the UK and Europe, guidelines recommend those with poor INR control as measured by time in therapeutic range (TTR) < 65% should be considered for alternative anticoagulation therapy [20,21]. Special focus is therefore required for those who are switched from VKAs to DOACs as their experience with VKAs may lead to expectations as to what anticoagulation therapy is and what it requires.

Amongst those prescribed VKAs, research has demonstrated that although many patients find monitoring burdensome [22], a significant number derived confidence from monitoring, reassuring them of their control over their illness with many claiming they would be apprehensive about anticoagulants that required no such monitoring [23–25]. Research also shows patients rely heavily on the availability of specialist anticoagulation staff to manage their VKA therapy [23]. Regular access is not available within the current UK model of care where DOACs will be managed in primary care and patients only gain access to specialists following referral. Studies assessing patient preferences for ideal anticoagulants demonstrated patients prefer regimes more akin to DOACs with simplified/fixed dosing regimens and limited monitoring, placing high value on the convenience of the treatment [26,27]. However, elsewhere patients ranked convenience as insignificant compared to risks of bleeding or thrombosis, suggesting they placed high value on VKA treatment and the associated monitoring [28]. Importantly, much of this research was undertaken prior to the widespread availability of DOACs and the regimes presented to patients were hypothetical, therefore preferences may not translate into real practice.

The Switching Study is an ongoing programme of work evaluating the association between health and medication beliefs with adherence to anticoagulation, the protocol has been published previously [29]. In this sub-study, the real-world experiences of patients switched from VKA to DOAC were explored following a minimum of 12 months treatment with a DOAC through focus groups. The aims of this sub-study were to investigate: the status of VKAs in comparison to their other medication prior to the switch owing to the high degree of monitoring and engagement with services associated with VKAs, if there was any change in the perceived status of anticoagulation post

switch owing to the minimal routine management and engagement with services, adherence to DOAC 1 year or more after initiating therapy and patient preferences for service provision in the context of anticoagulation.

## 2. Methods

Patients recruited into the Switching Study who had been switched from VKA to DOAC due to low TTR prior to November 2015 and therefore would have been prescribed it for greater than one year at the time of the focus group, were invited to participate in a focus groups at the anticoagulation clinic they were treated. In brief, as part of the broader study patients were seen in clinic at the point of switching to DOAC. This approximately 45-minute consultation explored issues surrounding VKA use; patients were counselled on DOACs and consented. Patients had a further 3 clinic appointments on average lasting 15 to 20 min at months 1, 2 and 12 after switching. The South London model of care states patients would initiate DOAC therapy in secondary care and be discharged to primary care after 3 months.

Eligible patients for this focus group sub-study were sent invitation letters and asked to indicate their intention to participate by returning a response form or by contacting a member of the research team. A target of 8 participants for each focus group was set as this is a manageable number for conducting focus groups whilst also allowing for a range of patients and views to assess [30]. In November 2016, four focus groups were conducted, across the two anticoagulation clinics at King's College Hospital NHS Foundation Trust, London: Denmark Hill (DH) and Princess Royal University Hospital (PRUH) sites (Fig. 1). A target duration of 90-minutes was set for each session. Patients were offered a retail voucher worth £30 for their participation. The focus groups explored four themes.

1. The value patients placed on VKAs compared to other medications prescribed.
2. Experiences with DOAC therapy, particularly post discharge from the anticoagulation clinic.
3. Adherence to DOACs following discharge from the anticoagulation clinic.
4. Patient preferences for long-term anticoagulation monitoring and service provision.

The sessions were conducted by an anticoagulation pharmacist and

psychologist as facilitators. Patients were unfamiliar with the facilitators, who were not involved in their care, and participants were unaware the facilitators were health professionals with expertise in anticoagulation. All facilitators had experience in conducting focus groups and/or had received training prior to this research. There was 1 female and 1 male facilitator in each session. Anticoagulation specialists facilitated so that erroneous views expressed by participants regarding anticoagulation, that might have been believed by others could be corrected at the end of the session. Patients were told the researchers were interested in their individual experiences and views to help improve future services, that it was in no way a test and their comments would not affect their future care.

All sessions were audio recorded, transcribed verbatim and entered into *NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 11, 2015* for qualitative analysis. A framework analysis methodology was employed, which is a form of thematic analysis providing descriptive explanations of data in relation to themes extracted from that data [31]. Transcripts were coded by JKBA and a coding manual generated which was then validated by JC. As part of the validation process, the validator was to bring to light any un-coded themes and the coding process would be repeated to ensure saturation of the data. Each coder operated independently however on completion the coders discussed the data and coding manual to provide quality assurance of the analysis and ensure there were no inconsistencies. Once validated, a framework matrix was developed and themes were extracted.

This study was reviewed and approved by the London-Dulwich Research Ethics Committee (13/LO/1468) and King's College Hospital NHS Foundation Trust research and development (KCH14-111).

### 3. Results

#### 3.1. Participants

Invitations were sent to 108 patients of whom 30 (28%) declared their intention to be considered (Fig. 1). As only one participant attended the DH VTE session, it was conducted as a semi-structured interview using the same topic guide as for the focus groups. For patient characteristics including stroke and bleeding risk [32,33], see Table 1. Amongst the AF cohort, only patient AF 9 had a history of stroke, all other AF patients were prescribed anticoagulation for primary prevention of stroke.

The transcripts were coded by JKBA and during validation no themes or codes were added by JC, indicating saturation of the data.

#### 3.2. Qualitative themes

Six key themes emerged from the analysis:

- Indication Specific Anticoagulation Prioritisation
- VKAs: A Necessary Inconvenience
- DOACs: the Anticoagulant of Choice
- Monitoring DOAC therapy
- Adherence to DOACs
- Provision for Access to Specialist Services Long Term

Further illustrative examples of participant responses can be seen in supplementary materials.

##### 3.2.1. Indication specific anticoagulation prioritisation

When asked where warfarin ranked amongst their medications, AF patients generally reported it was no more important than most of their medications, that VKAs were one of several medications needed to manage their cardiac condition. Although frequent testing and dose changes were considered inconvenient, the profile of VKAs was not raised in these patient's minds relative to other therapies.

**Table 1**

Summary of participant characteristics > 1 year into DOAC therapy.

Code name	Site	Age	Gender	Treatment	CHA <sub>2</sub> DS <sub>2</sub> VASc	HAS-BLED	Duration of VKA Therapy (weeks)
VTE 1	PRUH	63	Female	Rivaroxaban	N/A	1	66
VTE 2	PRUH	66	Male	Rivaroxaban	N/A	2	194
VTE 3	PRUH	44	Male	Rivaroxaban	N/A	2	112
VTE 4	PRUH	77	Male	Apixaban	N/A	2	51
VTE 5	DH	54	Male	Rivaroxaban	N/A	1	102
AF 1	PRUH	74	Male	Apixaban	4	4	105
AF 2	PRUH	59	Female	Apixaban	4	3	45
AF 3	PRUH	66	Male	Apixaban	2	3	20
AF 4	PRUH	77	Male	Rivaroxaban	3	2	28
AF 5	PRUH	78	Male	Apixaban	5	4	264
AF 6	PRUH	71	Male	Apixaban	3	3	146
AF 7	PRUH	64	Female	Rivaroxaban	3	1	223
AF 8	DH	70	Male	Rivaroxaban	2	3	76
AF 9	DH	69	Male	Rivaroxaban	4	3	254
AF 10	DH	89	Male	Apixaban	3	2	307
AF 11	DH	72	Female	Apixaban	4	3	166
AF 12	DH	80	Female	Apixaban	3	3	78
AF 13	DH	53	Female	Apixaban	3	1	26
AF 14	DH	60	Male	Apixaban	1	3	25
AF 15	DH	57	Female	Rivaroxaban	4	3	278

"I think that they are quite important, you know, tablets that I take for my heart and the angina and all that. It is important to take them all. It's just that I think with warfarin it's just a pain, yes, in the way it works, you know." Patient AF-2

Conversely, VTE patients claimed to prioritise VKA therapy. Having experienced at least one thrombotic event previously, relying on VKAs to treat and prevent further thrombi.

"Um. Yes. Probably, because the whole sort of concept of having a blood clot and what can happen is quite sort of frightening, yeah so to me it [warfarin] was more important." Patient VTE-1

"Yeah, yeah because I am very, very concerned. If you miss it, it means you are going to get a clot. And I don't know if it has anything to do with it, because my thigh was swollen and it was also coming up to my lungs. And that also frightened me. So, when they said warfarin, I made sure that I took it." Patient VTE-4

##### 3.2.2. VKAs: a necessary inconvenience

All patients recognised the need for long-term anticoagulation, with no patient questioning the necessity of their treatment; patients did however express complaints about their treatment. The main objection to VKAs was the cumbersome nature of therapy. All patients had low TTR at the point of switching, requiring more tests than the average patient. Testing was the most frequently cited complaint. Testing was particularly difficult for those in employment who either disrupted work to get tested or delay their testing to satisfy their work commitments. Proximity to testing centres was a significant issue for some patients who travelled some distance to be tested. There were also patients who reported having to wait in the blood test facility for long periods of time.

"I appreciate the things that can happen with taking warfarin, because it's like a preventative for irregular heartbeat and all that... And take it at a certain time, your intake of food is rather restricted and all that... a certain amount always. And I'm very glad I missed that, because I was told that every time I take blood tests I'm 30% over or under" Patient AF-3

### 3.2.3. Monitoring DOAC therapy

Patients appeared to struggle with the paradigm shift moving from VKAs to DOACs, specifically regarding the nature of oral anticoagulation monitoring. Many found it difficult to understand why VKAs needed monitoring so frequently and DOACs did not. Within this was also an expectation that such monitoring would indicate treatment efficacy; despite understanding the key parameter being reviewed with DOACs was renal function, for many this seemed incongruous with what they previously knew of anticoagulation. Patients reported they resorted to trusting health professionals knew what they were doing and they would not be at a high thrombotic risk.

“I thought well, why were all these checks necessary when I was taking warfarin? And why now do I go for a blood test once every six months? And I thought, well, what's happening in there now that happened with the warfarin? How does it regulate itself automatically? If the clotting agent or whatever it was going up and down like crazy with warfarin, but it wasn't with apixaban [...]” Patient AF-6

Expectations and preferences regarding monitoring DOACs varied largely depending on their indication for anticoagulation. VTE patients were eager for efficacy monitoring to provide reassurance regarding thrombotic risk. Tests akin to INR were frequently referred to as being desirable. They felt uneasy about not knowing how their blood was clotting and the key monitoring taking place was related to renal function. By contrast, AF patients key concern with regards to monitoring was to ensure that therapy was safe, with low risk of adverse effects and that they would be on the correct dose.

“I mean I actually understand that the blood test that you have done is nothing to do with INR, it's a kidney function test I think because it's processed through the kidneys. So again, there's no INR about it but there is that kind of feeling that you know; how do you know? Even if someone said, have your INR done once a year, I would be happy with that.” Patient VTE- 1

### 3.2.4. DOACs as the anticoagulant of choice

Despite concerns surrounding monitoring, patients emphatically preferred DOACs. Reasons were often presented in context of hindrances with VKAs such as frequent testing, dose changes, dietary restrictions and alcohol interactions. Furthermore, some patients described anxiety from fluctuating INRs and were glad this was no longer a feature of their treatment.

“It helps a lot, it helps a lot, it gives you the freedom, because as you were saying you are restricted in eating your greens and those sorts of things. But with this one you can eat whatever you want. I haven't gone to drinking yet, but probably there's room for me to drink.” Patient VTE-4

When asked whether they wished to return to VKAs treatment, no patient indicated they would. However, patients acknowledged that VKAs were no less effective than DOACs, stating “it just didn't seem to work for them”, or they “just couldn't get it to regulate”.

### 3.2.5. Adherence to DOACs

Most patients self- reported to be highly adherent to DOACs. Whilst some claimed emphatically they had never missed a dose, many suggested they might take a dose later than scheduled rather than completely missing it, whereas previously with VKAs they would have been hesitant to do so. Some patients utilised multi-dose devices such as pill boxes to help them keep track of their medication, others used mobile phone reminders or relied on family members. Most patients reported DOACs fitted in easily with established medicine taking routines, contributing to their high adherence.

There was agreement that missing a single dose would do little harm provided it was an isolated incident. It was widely acknowledged that

frequently missed doses would place them at significant thrombotic risk.

### 3.2.6. Provision for access to specialist services long term

There were an array of responses regarding preferences for long-term monitoring and follow up. A minority stated that there need not be any follow up unless there was a clinical need, others preferred an annual or biennial review with an anticoagulation specialist, whilst a minority felt this should be conducted by a general practitioner (GP).

The majority of participants stated a preference for some form of long-term follow up to monitor their therapy. Those preferring a specialist anticoagulation setting did so as they felt that expertise was required to manage DOACs. Some expressed a lack of confidence in primary care practitioners effectively managing DOACs. For some this was due to previous experience with primary care providers related to their anticoagulation, for others it was based on a perceived ambivalence from their GP. At the time the focus groups were conducted, several patients were due their routine renal function monitoring. Some patients stated that they had not been asked by their GP to have blood tests, while others who did have tests complained that they were not informed of the outcome of the blood tests, having no conversation with their GP about what this means for their anticoagulation therapy for the upcoming period.

“With the warfarin, they're [GP] spending more time talking to you about it but when you talk to them about rivaroxaban, it's like, they'll be standing there, turning the box around and looking at it... So, when they then start talking to you about it, you're not picking up confidence in what they're trying to explain to you... I think I know more about it than he does... Well, with this modern medicine [DOAC], I've seen him, while I'm talking to him, looking at Google. Googling up this [drug]...” Patient VTE-5

Furthermore, there was a suggestion that phone access to a dedicated anticoagulant service would be of value in case patients had questions surrounding their therapy or required advice relating to adverse events. When asked if they were likely to use such a service, many declared that they would, should they need it and would utilise it as first line rather than contacting their GP.

## 4. Discussion

This study provides valuable insight into patient experiences following the switch from VKA to DOAC. Focussing on this patient group, who were switched specifically due to low TTR is of importance as UK and European guidance suggests patients with TTR < 65% should be considered for DOAC therapy [21]. For healthcare providers, there is therefore an imperative to understand their experiences and tailor services to address patient needs.

Although experiences regarding difficulties in VKA management are widely known, they nonetheless deserve attention. Frequent testing is unavoidable in ensuring safe anticoagulation; however, the provision and setup of testing centres can be addressed. Similar issues have been raised in research elsewhere [24,25]. Capillary testing is a quick and easily applicable alternative to venous sampling. Venous sampling is time consuming for patients, furthermore in those for whom acquiring venous access is problematic, it can be lengthy and painful [34]. This is particularly important for elderly populations, which the majority of AF patients are [35,36]. Similarly, for those who rely on health visitors attending to the patient in their home, capillary testing may be more economic and convenient.

The vast majority of patients reported high levels of adherence to DOACs, with no patient reporting they deliberately omit doses. In most cases, when missed doses did occur, the remainder of the patient's medicines were also missed. All patients were prescribed at least one medication in addition to their anticoagulant. Therefore it is likely that all participants had some form of established medicines taking routine



which would aid adherence, this is consistent with previous research [17]. To ensure optimal adherence to DOACs in patients prescribed additional medicines, perhaps efforts should be directed towards addressing adherence in the context of an entire regime rather than a single drug. This does not negate addressing knowledge deficits or patient beliefs surrounding their illness and anticoagulation in the consultation as this can be vital in ensuring good adherence [25,37]. Furthermore, research demonstrates AF patients value these discussions when considering anticoagulation [38,39]. It must be noted that patients were invited to discuss their adherence and no validated adherence measure was used, it is possible that patients may have inaccurately reported their adherence.

On realising doses had been missed the majority of patients reported they would take their dose as soon as they realised whilst a minority stated they would wait until the next scheduled dose. In their anticoagulation knowledge questionnaire study, Desteghe and colleagues found that 57% of DOAC patients did not know how to appropriately manage missed doses [40]. During initiation it is vital patients are informed of best course of action in these scenarios and that this be reinforced at subsequent consultations [41]. A range of techniques were adopted by participants to aid adherence: mobile phone reminders, multi-dose devices such as self-filled dosette boxes to assist keeping track of what was taken and social support from family members was also common. This is in keeping with research elsewhere with AF patients recommending anticoagulation services provide support with memory aids [39].

It is clear our patients valued anticoagulation differently depending on the indication for treatment. Whilst it is tempting to assume that perceptions regarding a single drug will be similar across different populations, our VTE patients valued and prioritised anticoagulation more than AF patients. This may be intuitive as the VTE patients experienced multiple thrombotic events where anticoagulation was the active treatment. This experience may enable them to recognise the value of prophylactic anticoagulation more readily. According to the COM-B model of adherence which suggests that medicines use is a behaviour influenced by one's capability to adhere, opportunity to adhere and motivation to adhere [42,43]; VTE patients would have relatively higher motivation due to their prior experience. Whereas in our AF sample, only one participant had a history of stroke and therefore motivation may be lower in patients prescribed anticoagulation for primary prevention [16,44].

Patients reported concerns regarding the frequency and nature of monitoring with DOACs in comparison to VKAs. Although all patients were informed of the rationale for type of monitoring DOACs require and the differences with VKAs at initiation, this was either not retained long term or was insufficient. Perhaps dedicating time in consultations to address monitoring both verbally and in writing would be valuable. Patient expectations with regards to monitoring, i.e. VTE patients expecting efficacy monitoring and AF patients largely expecting safety monitoring; aligns significantly with the value patients placed on therapy. Research amongst VTE patients demonstrates that the more thrombotic experiences the patient has, the greater the anxiety and perceived risk of further thrombosis [45]. VTE patients were most concerned with preventing thrombosis and wanted tests to inform their risk was low. For AF patients who placed lower value on their anticoagulation, whilst recognising its necessity, their priority for monitoring was that treatment did no harm. This replicates previous research finding AF patients value anticoagulation safety more than efficacy [46], especially when made explicitly aware that major bleeding can cause death [47]. Elsewhere, large variation has been found in AF patient's willingness to accept major bleeding in stroke prevention [48]. Had there been greater representation of stroke sufferers amongst our AF participants this finding may have been different. However, this dichotomy between AF and VTE patients is of value when considering that a large proportion of anticoagulated AF patients are being treated for primary prevention and will not have experienced a thrombotic event.

A large proportion of patients derived confidence from being managed long-term by a specialist anticoagulation clinic rather than in primary care, even though the monitoring required can be handled in primary care. This seemed based on the perception DOACs as "new" and knowledge about them is not mainstream, as well as negative experiences amongst some participants with GPs around DOACs. As uptake of DOACs increases, models of care are more likely to utilise primary care far more than with VKAs. There is therefore a pressing need that primary care clinicians become upskilled with respect to DOACs. Research demonstrates that both primary and secondary care clinicians were unable to recognise DOACs as anticoagulants or identify risks associated with them [49,50]. Furthermore, in secondary care, drug related problems with DOACs have been found to be significantly high, a key factor being limited knowledge amongst clinicians [51]. Patients reporting they would preferentially contact the anticoagulation clinic over their GP for anticoagulant related advice suggests that provisions should be made for patients to consult specialists should the need arise.

The findings of this research are to be incorporated into a subsequent sub-study of the Switching Study. Using the evidence base generated from the focus groups as well as other aspects of this body of research, an intervention to support patients who are newly switched from long-term VKAs to long-term DOACs for SPAF or secondary prevention of VTE will be piloted.

## 5. Conclusion

One year on from switching from VKAs to DOACs due to low TTR, patients reported to be adherent to DOAC therapy. Whilst VTE patients placed greater value on anticoagulation, this did not result in a greater level of adherence. Patients derived confidence in being managed by specialist services and largely wished to have long-term monitoring through that specialist service rather than through primary care, although their expectations for what monitoring would involve varied.

## 6. Limitations

This study only examined experiences of those with a history of VKA use. Although some findings such as the value patients place on anticoagulation may be applicable, not all findings may translate to anticoagulation naïve patients prescribed DOACs. Furthermore, our sample size was small and our participants were a self-selecting group of patients who volunteered to participate. It is possible that our participants may not be representative of the overall anticoagulated population.

## Author contributions

Data collection was conducted by JKBA, JPP and VA. Data analysis was conducted by JKBA and JC. This manuscript was drafted by JKBA, was subsequently revised by JPP and VA and reviewed by all other authors.

## Disclosures

Professor Arya has received honoraria for lectures and travel from Bayer, Boehringer Ingelheim and Pfizer, and awards for investigator sponsored research from Bayer and Covidien. Dr Auyeung and Dr J.P. Patel have received investigator initiated research funding from Bayer. Dr Vadher has received travel grants and event sponsorship from Boehringer-Ingelheim and Bayer. Dr Roberts has received speaker fees and a travel grant from Bayer. Dr R. Patel has received honoraria from Bayer, Boehringer-Ingelheim, Daiichi-Sankyo and BMS- Pfizer. Alison Brown has received a travel grant from Daiichi-Sankyo. John Bartoli-Abdou and Jacob Crawshaw have no disclosures to declare.

## Acknowledgements

The Switching Study is funded by an investigator initiated grant from Bayer PLC.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.thromres.2017.12.021>.

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